Hypercalcuria and Metabolic Bone Disease

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• *Hypercalcuria leading to nephrocalcinosis and nephrolithiasis may be secondary to a number of causes. In most instances, the history, physical examination, a few simple laboratory tests and x-ray study of the bones will reveal the true primary diagnosis. Specific treatment, if instituted early, will result in a satisfactory response and prevent the progression of renal complications.*

THE ASSOCIATION of hypercalcuria, renal calcium deposition and bone disease serves to bind together a number of otherwise unrelated diseases. The development of nephrolithiasis and nephrocalcinosis in these syndromes is largely secondary to disturbances in the gain and loss of calcium and phosphorus. Because of the associated errors in calcium and phosphorus metabolism, bone disease commonly accompanies the renal lesions either as a cause of increased loss to the blood and urine or as a secondary effect of decreased stores of available calcium.

This group of diseases frequently comes to the attention of urologists because urolithiasis may be the predominant or only symptom while the true etiologic defect, an aberration in the calcium metabolism, remains obscure. Although the statistical incidence of urolithiasis secondary to metabolic disease comprises only a small percentage of the total number of cases in which there are renal stones, it is nevertheless important to recognize the basic disorder not only to prevent recurrence or progression of calculous disease but to correct the underlying lesion. Regardless of the cause, the end results of hypercalcuria are the same so that the urologic manifestations remain relatively constant. The diagnosis in these conditions may be suspected by determining the presence of hypercalcuria. This is done by measuring the 24-hour urinary calcium excretion while the patient is on a regulated low calcium intake.

The renal disease can consist of either nephrolithiasis or nephrocalcinosis. Nephrolithiasis is of course the formation of calculi in the calyces or pelvis of the kidney (Figure 1). Nephrocalcinosis is calcification in the renal parenchyma and is a more serious sequel since calcium deposits fill the collecting tubules of the kidney and renal insufficiency occurs more rapidly (Figure 2). Calcium phosphate casts in the urine are not indicative of this disease since they occur normally in alkaline urine of patients who ingest large quantities of calcium and phosphorus. These casts disappear when the urine becomes acid.[1] Patients may have either nephrocalcinosis or nephrolithiasis but most often do not have both.[2]

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BASIC CONSIDERATIONS

The skeleton contains 99 per cent (900 to 1,500 grams) of all the calcium in the body, and normal daily deterioration of the bones leads to the urinary

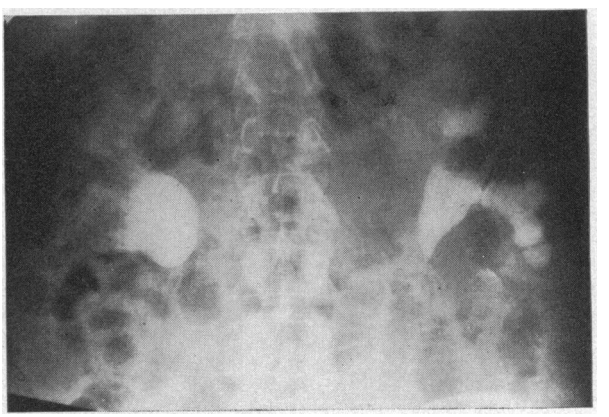

Figure 1.—Nephrolithiasis. Bilateral staghorn calculi filling the renal pelvis and calyces.

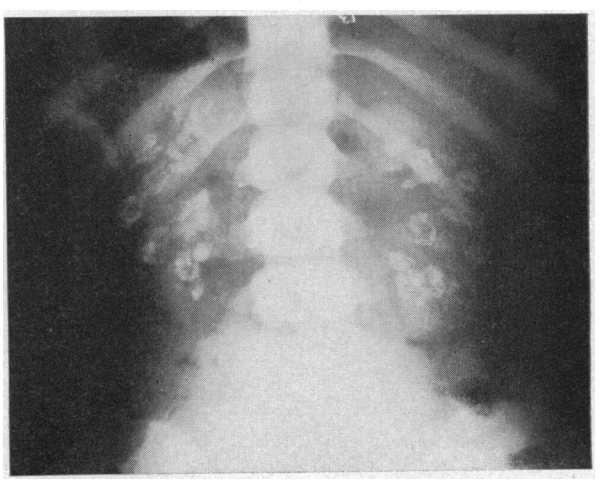

Figure 2.—Nephrocalcinosis. Diffuse parenchymal calcification in the tubules of a 7-year-old girl.

and fecal excretion of about 300 mg. or more of calcium when there is an average dietary intake of a half gram or more. Of the total bone ash, 85 per cent is calcium phosphate and 12 per cent is calcium carbonate. The normal serum calcium values are 9 to 11 mg. per 100 cc. and the "renal threshold"—the serum content below which calcium is not excreted in the urine—is 7 mg. per 100 cc. About one-fourth to one-third of the calcium intake is normally excreted in the urine. One-half the total serum calcium is ionized, soluble and diffusible. This fraction is subject to parathyroid control. Most of the remaining calcium is bound to protein. No calcium is found in the erythrocytes.

When there is only a slight increase in the total serum calcium it is important to measure the total serum protein. The amount of ionized calcium reflects the degree of hyperparathyroidism while the amount of calcium bound to protein is determined by the amount of protein. Thus the ionized calcium may be slightly high with mild hyperparathyroid disease. Yet if the total protein is low, the total serum calcium will be normal. The amount of ionized calcium can be determined by the use of a chart calculated by McLean and Hastings[13] if the amounts of serum calcium and serum protein are known (Chart 1).

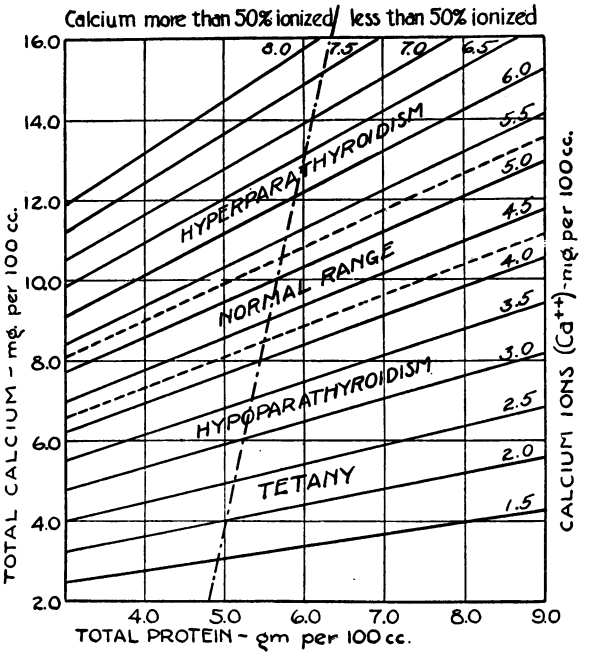

Chart 1.—Calculation of ionized calcium from total serum calcium and protein. (From McLean and Hastings.)

Of the average 670 grams of phosphorus present in the body, 80 per cent is in the skeleton.[16] Approximately two-thirds of the phosphorus intake normally goes out in the urine, this being almost the entire phosphorus excretion from the body. The inorganic phosphorus, which is the ionized form and is under parathyroid influence, represents one-fourth the total serum phosphorus and is normally 3 to 4.5 mg. per 100 cc. of serum.

There is a definite equilibrium which the body maintains in terms of calcium and phosphorus so that an increase in the ions of one will result in a decrease in the other. This equilibrium is such that the product of the milligrams per cent of total serum calcium to serum inorganic phosphorus is between 30 and 40 for adults and slightly higher for children. Calcium and phosphorus also influence each other in terms of absorption from the gastrointestinal tract. With a high calcium intake less phosphorus is absorbed since insoluble calcium phosphate is formed. When there is a low calcium diet, phosphorus absorption will be high.

An important consideration is that bone is a living tissue rather than merely a structural support composed of inorganic materials. It is a protein mass containing calcium-phosphate-carbonate salts. There is a constant formation of new bone with production of protein matrix and deposition of calcium salts. The matrix or osteoid is produced by the osteoblastic cells which also produce alkaline phosphatase (an enzyme which releases phosphate from organic complexes). Simultaneously, continuous bone resorption is occurring due to wear and tear and the osteoclastic cells are active in destroying bone. Acidosis increases solubility and increases bone resorption. Since phosphorus is excreted with the calcium, most of the calculi formed are of the calcium phosphate variety. These have a tendency toward staghorn formation.

CAUSES OF HYPERCALCURIA

There are essentially four causes of hypercalcuria as described by Reifenstein:[16] (1) Excess gastrointestinal absorption of calcium; (2) excess bone resorption; (3) decreased bone formation; (4) excess renal excretion of calcium.

Excess gastrointestinal absorption. Calcium is absorbed in the proximal portion of the small intestine possibly because this portion has a more acid medium and calcium solubility increases with acidity. Increased absorption occurs with excessive dietary intake (as in ingestion of large amounts of milk) and with vitamin D poisoning from excessive medication over prolonged periods. Vitamin D acts to increase calcium absorption from the gastrointestinal tract and to increase urinary phosphorus excretion. By contrast, decreased calcium absorption from the bowel may be effected by (a) fatty diarrhea with the formation of calcium and magnesium soaps and the loss of vitamin D, which is fat-soluble; (b) increased phosphates in the bowel, forming insoluble calcium phosphate. Increased fecal phos-

phate occurs in uremia where the diseased kidney cannot excrete phosphate, thus giving rise to hyperphosphatemia and increased intestinal excretion.[19] It also occurs in association with diets rich in phosphate with little calcium. With increased calcium absorption, the excess intake is compensated by excess urinary excretion of calcium.

Excess bone resorption. Excess calcium loss by resorption of bone occurs with hyperparathyroidism, acidosis, osteolytic metastases, multiple myeloma, Paget's disease and sarcoidosis. The calcium released from the bone enters the circulation and is excreted through the urine.

Primary hyperparathyroid disease causes a classical syndrome. Increased production of parathyroid hormone causes hypophosphatemia which leads to hypercalcemia. Albright and co-workers[2] found that excess hormone causes (a) increased excretion of phosphate in the urine by decreasing the renal threshold for phosphate excretion and (b) increased activity and hyperplasia of the osteoclasts, thus causing increased bone loss of calcium and phosphorus. These changes then give rise to the following sequence of events:[2] (1) hyperphosphaturia; (2) hypophosphatemia; (3) hypercalcemia; (4) hypercalcuria.

With the excess excretion of calcium and phosphorus, nephrolithiasis (or calcinosis) occurs, and then renal insufficiency. Polyuria and polydipsia occur due to the action of parathyroid hormone as well as from tubular damage which occurs from calcium precipitation.

Since the excess calcium comes from both the bones and the food, bone changes may not be demonstrated if the dietary ingestion of calcium has been adequate. In many instances, the renal lesions are the only objective findings. In more advanced cases, the blood changes of increased calcium and decreased phosphate are evident, but in early or mild cases, only the urine will reveal the diagnosis.

In all cases of recurrent or multiple calculi, particularly of the calcium phosphate variety, the 24-hour urinary calcium excretion should be measured. This is done on the fourth day of a diet that contains less than 175 mg. of calcium daily. If the 24-hour calcium excretion is more than 200 mg., hyperparathyroidism should be strongly considered. The Clark-Collip[8] method for calcium determination gives an accurate quantitative measurement. The Sulkowitch test is helpful but gives only a rough qualitative estimate of calcium excretion.[3]

The serum alkaline phosphatase will be elevated only if there is associated bone disease (osteitis fibrosa generalisata). Hence, this test is not diagnostic of hyperparathyroid disease and it indicates only the degree of bone involvement. In early bone lesions, only the skull and the lamina dura around the teeth may be affected. However, where there is extensive bone disease, as roentgenographically observed, if the alkaline phosphatase is not elevated, hyperparathyroid disease may be ruled out. In patients who drink milk or increase the ingestion of calcium, the bone lesions may regress but the underlying disease remains the same.

Thus the major diagnostic points are excess urinary calcium excretion, elevated serum calcium and decreased serum inorganic phosphorus. Resorptive bone lesions are associated with elevated serum alkaline phosphatase. Treatment consists of surgical removal of the parathyroid adenomata. The immediate postoperative period may be dangerous in patients with high serum alkaline phosphatase. Tetany may occur since the calcium leaves the blood for deposition in the bones as calcium phosphate. These patients should have a high calcium intake, usually best given intravenously as calcium gluconate. Phosphate should be withheld, since lack of it prevents deposition of calcium as calcium phosphate.

Chronic acidosis is generally associated with increased bone resorption. This may be at least in part due to the increased solubility of calcium and phosphate in an acid medium so that a more rapid rate of dissolution occurs. When the acidosis is associated with renal disease, secondary hyperparathyroidism often occurs. According to Albright and Reifenstein,[2] the sequence of events is (a) renal insufficiency, (b) phosphorus retention, (c) tendency to low serum calcium as an adjustment to an elevated serum phosphorus and (d) parathyroid hyperplasia to meet this tendency. This condition is called "renal rickets" (improperly) because the epiphyseal changes which occur in this syndrome are somewhat like those of rickets. There is widespread renal damage in such cases and the calcium and phosphorus aberrations are due to both tubular and glomerular disease.[2] First the tubular disease prevents the tubular production of ammonium ion and hydrogen ion. Then acid urine cannot be excreted because no ammonium or hydrogen ion is produced to ferry the acid radicals. To substitute for these acid-neutralizing ions, calcium is excreted in the urine. This lowers the serum calcium and also leads to parathyroid hyperplasia. Ordinarily, parathormone would cause excess urinary excretion of phosphate but this does not occur because of the defective glomeruli. Hence the high serum phosphorus remains. This high serum phosphorus is conducive to the prompt laying down of calcium in the bone, particularly in the trabeculae. Thus, in these circumstances the acidosis causes the bone disease, whereas in primary hyperparathyroidism the excess hormone causes the bone disease. The acidosis and renal disease should be treated and the bone will respond. The administration of alkaline salts such

as sodium citrate will correct the acidosis. The addition of citric acid is helpful since the intestinal contents become more acid and calcium absorption is increased.[2] The citric acid is metabolized after absorption and leaves free base. Large amounts of vitamin D and calcium in addition will relieve the bone disease. The renal failure should also be treated.

In chronic acidosis and secondary hyperparathyroidism there is thus primary renal disease with elevated creatinine, urea, sulfate, phosphorus and a decreased phenolsulphophthalein excretion. There is both a loss of base and a retention of acid ions. In primary hyperparathyroidism serum phosphorus is low and serum calcium high. In secondary parathyroid disease, the serum phosphorus is high and the serum calcium is low or normal and there is always associated bone disease with elevated alkaline phosphatase (osteomalacia or osteitis fibrosa generalisata).

Secondary parathyroid hyperplasia occurs not only in kidney disease with a high phosphate but in all types of osteomalacia or rickets, pregnancy and states of calcium deprivation.[2] In all of these there is a tendency toward low serum calcium, which stimulates the parathyroids.

Metastatic malignant disease of the osteolytic type will occasionally cause hypercalcemia, hypercalcuria and nephrolithiasis. In these cases it is likely that the malignant process dissolves the calcium and allows it to pour into the blood more quickly than the kidneys can excrete it. The serum phosphate is most often normal or occasionally high in these cases and it is only rarely low. Diagnosis can be made by the typical roentgen appearance of the lesions and the presence of malignant change. In general, treatment of the underlying metastasis will result in improvement of the urologic complications. Hermann and co-workers,[9] however, observed some instances in which androgens and estrogens given for osteolytic metastatic breast carcinoma caused hypercalcemia and subsequent azotemia. This was in bedridden patients. Hypercalcemia induced by sex hormones has not been observed in ambulatory patients. Apparently, the steroids mobilized calcium, which was excreted through the kidneys, giving rise to nephrocalcinosis and renal insufficiency. This action is similar to that occurring in parathyroid hormone and ergosterol therapy.

In multiple myeloma also there may be a high content of calcium in the serum and the urine, but in most instances the phosphate and the alkaline phosphatase is normal. The changes appear to be a direct effect of the lesions acting on the bone. Diagnosis may be made by the roentgen appearance of the bones, the presence of plasma cells in the blood, excess blood globulin and examination of material aspirated from sternal puncture. Bence-Jones protein may be present in the urine.

Paget's disease (osteitis deformans) seldom causes hypercalcuria and stones, but it may if there is rapid progress of the bone lesions and particularly if the patient is immobilized. This is a "spotty" disease in which areas of bone destruction occur.[16] These weakened areas undergo increased stress and, because of this, osteoblastic activity increases. There then occurs very active bone repair with actual overgrowth of bone and an increase in the density and coarseness of the trabeculations. Because of this pronounced osteoblastic activity, the alkaline phosphatase is greatly elevated. Diagnosis can be made by roentgen observations and the very high phosphatase. In most cases the serum phosphorus and calcium are normal. Treatment of patients with this disease who must be immobilized consists of the Shorr regimen with low calcium and low vitamin D intake. Early ambulation and good fluid intake are stressed. For ordinary Paget's disease without hypercalcemia and renal lesions, the excess bone resorption is treated by a high intake of calcium, phosphorus and vitamin D.

In sarcoidosis (Boeck's), nephrolithiasis and nephrocalcinosis are again secondary to hypercalcemia and hypercalcuria.[10] Granulomatous infiltration of the kidney does not appear to be the major factor in producing renal insufficiency. This condition may be mistaken for hyperparathyroidism clinically but the serum phosphorus is normal and the alkaline phosphatase may be normal or slightly elevated. Blood protein and globulin are usually high, and the bone lesions are mostly limited to the hands and feet and have a punched-out appearance. Management consists of reducing the calcium intake, making sure that fluid intake is adequate, and administration of corticotropin (ACTH) and cortisone. The cause of hypercalcemia in this condition is not clear. On the basis of balance studies showing that increased calcium intake caused decreased loss of calcium from bones, Albright and Reifenstein[2] expressed belief that it is due to some primary change in the blood that brings about an increase in its calcium content, rather than to the bone disease.

Decreased bone formation. This occurs when the bones are unable to avail themselves of calcium for the purpose of forming new bone and either osteoporosis or osteomalacia is produced. Osteoporosis represents a lesion of tissue metabolism in that the bone is unable to accept calcium even though it is readily available. Osteomalacia on the other hand is a defect involving calcium so that the calcium is not available to the bones. Differentiation of these conditions by roentgen appearance is not difficult when there is either pure osteoporosis or pure osteomalacia. In osteoporosis, there is a diffuse calcium loss

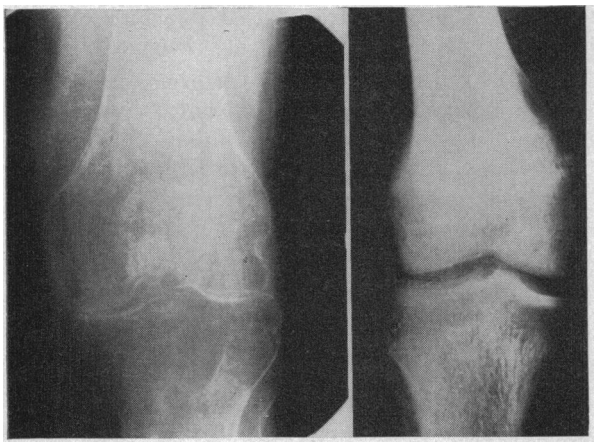

Figure 3.—*Left:* Pronounced osteoporosis in a patient receiving cortisone therapy. There is a diffuse calcium loss with only a thin surrounding calcified shell. *Right:* Pronounced osteomalacia in a patient with hyperparathyroidism. There is a prominent trabecular pattern with coarse and widespread trabeculation.

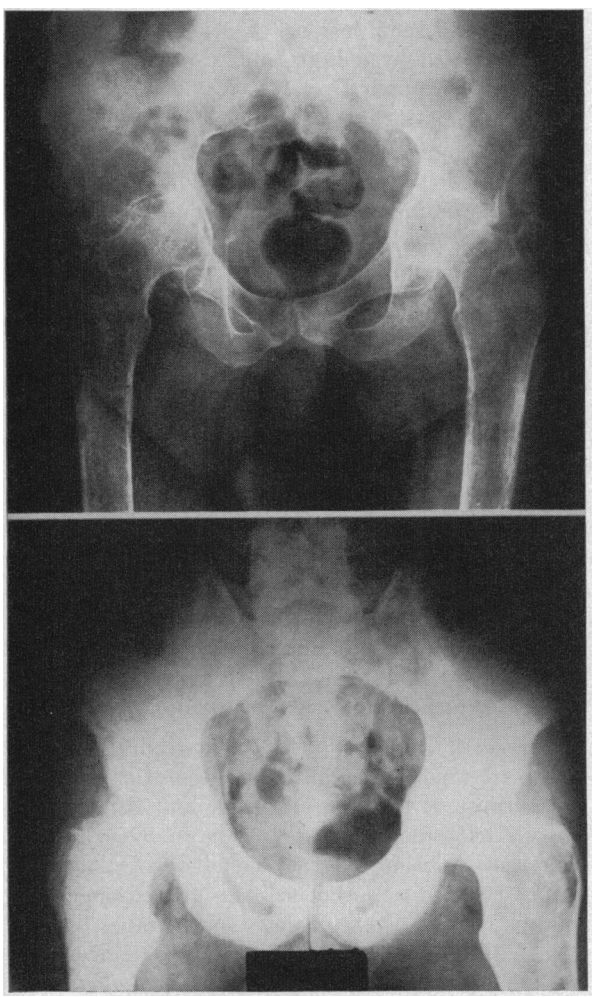

Figure 4.—*Upper:* Osteoporosis with diffuse calcium loss in the pelvis of the patient in Figure 3 (left). *Lower:* Osteomalacia with prominent primary trabeculation in the pelvis of the patient in Figure 3 (right).

so that only a thin surrounding shell remains. In osteomalacia, the trabecular pattern is prominent with coarse and widespread trabeculation. The laying-down of calcium in the trabeculae in osteomalacia may be explained teliologically in that the osteoblasts are active and deposit inadequate amounts of calcium in the primary supporting structure of the bone. Figures 3 and 4 show the washed-out appearance of osteoporosis and the prominent trabeculae of osteomalacia.

Osteoporosis occurs when the daily wear and tear of the skeleton exceeds the amount of new bone being formed. The causes of osteoporosis are outlined by Albright and Reifenstein[2] as follows:

I. Defect in osteoblasts.
   (a) Immobilization.
   (b) Postmenopausal—estrogen lack.
   (c) Congenital osteoblastic defect (osteogenesis imperfecta).

II. Defect in matrix.
   (a) Protein loss — malnutrition, scurvy, Cushing's syndrome and "alarm reaction."
   (b) Androgen loss—senility(?) eunuchoid states.

III. Defect unknown.
   (a) Idiopathic.
   (b) Acromegaly.

It is caused primarily by either a defect in the osteoblasts or a defect in the bone matrix so that these structures do not accept calcium even though it be present in the blood stream in large quantities. The calcium or phosphorus is not used by the bones but intestinal absorption continues. Thus, the large amounts of available calcium and phosphorus are excreted in the urine and there can occur hypercalcuria, hyperphosphaturia and sometimes alterations in the serum calcium and phosphorus. In most instances of osteoporosis, however, the serum calcium and phosphorus are normal.

Urologically, osteoporosis becomes disastrous in its acute form, as in association with enforced recumbency, immobilization of the body in a cast, or severe poliomyelitis. In these situations, with absence of the stresses that stimulate osteoblastic activity, bone matrix is not produced. Bone deterioration also occurs more rapidly with immobilization, particularly in young people, and it is not uncommon to observe bilateral staghorn calculi a few months after immobilization. Deitrick and co-workers[6] studied the effects of recumbency upon healthy men and found that the calcium content of the urine doubled. There was increased urinary phosphorus excretion without increase in the urinary volume. The fecal calcium excretion also increased.

Diagnosis of this condition is not difficult. Generally most changes observable roentgenographically occur in bones other than the skull. The patients usually can eat and move the head so that atrophy of disuse does not affect the skull and lamina dura. The serum calcium and phosphorus are usually normal; but, even in acute cases, when the calcium is elevated the phosphorus is high, not low, and the serum alkaline phosphatase is normal. In hyperparathyroidism, the serum phosphorus is low, the alkaline phosphatase is high and the earliest changes that can be seen roentgenographically occur in the skull and lamina dura.

Management should consist of early ambulation, particularly weight-bearing. The use of the oscillating bed when begun early is of value and has been shown to significantly decrease the abnormalities in calcium, phosphorus and nitrogen balances.[20] Weight-bearing may be accomplished even with the patient in casts by the use of a tilt-table which can be adjusted by degrees for gradual standing. Following surgical procedures, there should be maximum motion of all muscles even on the day of operation, and confining dressings such as abdominal binders should be avoided. Shorr's regimen for patients in prolonged recumbency has proven to be most valuable in preventing urinary calculi.[18] The regimen stresses the dietary restriction of phosphorus to less than 1,275 mg. per day. In addition to this, aluminum carbonate (Basalgel) or hydroxide is given in amounts adequate to maintain urinary phosphate excretion of less than 300 mg. daily. The average dose of Basalgel is about 30 to 40 cc. after each meal and at bedtime. This regimen is valuable in preventing the progression or recurrence of phosphatic calculi. Some investigators stress the value of androgens and estrogen to promote calcium and protein storage.[21] Butt and co-workers[5] demonstrated that hyaluronidase increases the protective colloids in the urine by releasing hyaluronate at the site of injection. This is excreted in the urine and reduces the tendency toward stone formation.[5] This observation has not been confirmed in our own clinic.

The more insidious forms of osteoporosis are less often associated with disturbances in the calcium balance, and urologic complications are few. Postmenopausal osteoporosis, probably the most common, is due largely to the loss of estrogen. Estrogens have been shown to have a stimulating effect upon the osteoblasts.[2] Therapeutically, response to estrogen is good but even better to combined estrogen-androgen therapy. Androgen speeds protein synthesis and leads to a positive nitrogen balance. In patients with disturbances in calcium metabolism, the urinary and fecal calcium and phosphorus excretions decrease with steroid treatment. Pain in the ribs and back disappears rapidly. In this condition, skeletal demineralization is limited mostly to the spine, ribs and pelvis; and typical "codfish" deformities due to pressure collapse of the vertebral body, with the nucleus pulposus pushing out into the soft bone, are to be seen roentgenographically. The skull and lamina dura are intact and the alkaline phosphatase, calcium and phosphorus are usually normal. In the early stages of postmenopausal osteoporosis, there may be an acute phase with hypercalcemia, hypercalcuria and renal stones.

Osteogenesis imperfecta does not concern urologists except in differential diagnosis. The congenitally defective osteoblasts form too little bone matrix. The patients have characteristic blue sclerae and nerve deafness. The serum calcium and phosphorus are normal and the alkaline phosphatase may be normal or slightly elevated.

Since the bone matrix is a protein substance, when there is a defect in the protein metabolism, the inadequately formed matrix cannot receive calcium and phosphate for deposition. This is particularly true in osteoporosis associated with malnutrition. In malnutrition there may be the additional factor of vitamin D deficiency. Scurvy leads to bone lesions because of the direct effect of ascorbic acid on the formation of bone matrix and on normal osteoblastic activity. The x-ray findings are typical.

In Cushing's syndrome, excess "S" or "sugar" hormone is produced.[2] This hormone is anti-anabolic and acts on all tissues, including bone. The most pronounced changes occur in the spine. The many characteristic features of this syndrome make the diagnosis clear-cut and the changes in bones and the kidneys are only incidental findings. Treatment of the bone lesions is the same as in Cushing's disease and depends upon whether it is due to adrenal hyperplasia, tumor or pituitary disease. Testosterone therapy is of value preoperatively along with potassium and a high protein diet to accelerate anabolic processes. Selye's "alarm reaction" and therapy with corticotropin and cortisone exert the same effect as does Cushing's disease.

Senile osteoporosis may represent merely an atrophy of bone with senescence or it may be a lack of production of androgens and estrogens. Treatment is the same as that for osteoporosis of the postmenopausal type. Steroid therapy has pronounced beneficial effect.

Idiopathic osteoporosis is uncommon. The cause of the disease is unknown but the findings are the same as those in osteoporosis from known causes. Treatment is difficult and there is no benefit from steroid therapy. In fact, this is a point of differential diagnosis.

Osteoporosis associated with acromegaly occurs occasionally and may be on the basis of hypogonadism.[2] Steroid therapy, particularly with estrogens, causes pronounced improvement. The bone disease

that occurs occasionally with hyperthyroidism may be secondary to increased catabolism causing increased bone breakdown and increased demands for protein, resulting in a protein deficit. In severe diabetes mellitus, osteoporosis may also occur due to protein deficiency plus acidosis.

Osteomalacia or "adult rickets" occurs when the bone matrix is normal but the calcium is not available for deposition. The level of inorganic phosphate may be too low to allow the calcium to be precipitated. Since the normal osteoblasts make every effort to calcify the bones, the serum alkaline phosphatase is high. The serum calcium and phosphorus levels may be normal or low. This condition is to be differentiated from osteoporosis, in which the serum phosphatase, calcium and phosphorus levels are normal, and from hyperparathyroidism in which the serum phosphatase and calcium are high and the phosphorus is low.

Since this condition occurs because of calcium lack, any situation where there is inadequate calcium absorption or increased calcium excretion will result in osteomalacia. The following causes of osteomalacia have been adapted from Albright and Reifenstein:[2]

(a) Lack of vitamin D.

(b) Renal acidosis { Renal tubular acidosis / Fanconi syndrome

(c) Idiopathic hypercalcuria

(d) Hyperparathyroidism, postoperative

Osteomalacia due to lack of vitamin D—which plays a part in calcium absorption—is rare in this country. Loss of D may be due to decreased intake, increased loss (steatorrhea) or resistance to vitamin D.

Renal tubular acidosis is a relatively common cause of osteomalacia and nephrolithiasis. In this disease, there is insufficiency of the tubules but normal glomeruli. The tubular lesion may be the result of pyelonephritis or may be congenital. The normal function of the tubule is to produce ammonium ion and hydrogen ion and to excrete acid urine. The loss of these functions results in a loss of neutralizing ions to ferry the acid radicals (chloride and others) out in the urine. To substitute for this loss, fixed base including calcium is lost in the urine and the acids are excreted as calcium or potassium salts. The tendency toward low serum calcium is adjusted by loss of calcium from the bones; and, owing to stimulation of the parathyroids, there is an increase in urinary phosphate with a decrease in the serum level. The sodium level remains normal, possibly because there is mild dehydration and renal tubular mechanisms act to conserve sodium and excrete potassium.[15] Hyperchloremic acidosis occurs, since excess base over fixed acid is lost, but the urinary pH remains above 6.0 despite the acidosis. The potassium and inorganic phosphorus serum levels may be normal or low. The serum calcium and nonprotein nitrogen may be normal and the alkaline phosphatase is elevated in proportion to the amount of osteomalacia. There are x-ray findings of osteomalacia (demineralization, pseudofractures) and nephrolithiasis and nephrocalcinosis. There may be a chronic acidosis and altered neuromuscular function. The urine contains a reduced amount of ammonium, and the titratable acidity is decreased. This disease is to be differentiated from "renal rickets" in which there is also glomerular damage and retention of phosphorus, sulfate, urea and creatinine.

This syndrome is thought by some investigators[11] to account for the hyperchloremic acidosis which frequently accompanies ureterosigmoidostomy, on the basis of tubular damage from infection and obstruction. Whether the hyperchloremia results from a tubular lesion or whether it is due to excess absorption of acid salts from the sigmoid in the face of poor renal function,[17] therapy consists of a high alkali intake, rectal tube drainage and measures aimed to improve renal function.

Treatment of osteomalacia and nephrolithiasis from tubular acidosis consists of the use of alkali and vitamin D. The administration of base, such as sodium bicarbonate, spares the calcium and prevents further loss. The vitamin D induces increased calcium absorption from the gastrointestinal tract. Calcium intake may also be increased. Once the bone lesions have healed, vitamin D should be discontinued. Response to therapy is dramatic. The bone lesions heal rapidly and in some instances the renal calculi are reduced.

The Fanconi syndrome produces acidosis as a result of increased urinary excretion of organic acids (possibly due to decreased tubular reabsorption). This lesion is rare. To ferry these increased acid radicals, the kidneys must secondarily excrete increased fixed base, and this results in excess calcium loss. The calcium loss causes a tendency toward a low serum calcium, which causes a parathyroid stimulation leading to increased urinary phosphorus, lower serum phosphorus and correction of the serum calcium. In this condition, to meet the increased demand for coverage of the acid excretion, the kidney steps up tubular production of ammonia and titratable acid (H^+). In renal tubular acidosis, the basic difficulty is tubular impairment with a decrease in ammonia and titratable acid.

The features of this hereditary disease are rickets and decreased growth, renal glycosuria, alkaline urine, increased amounts of organic acids, ammonia, phosphorus and calcium in the urine, pronounced hypophosphatemia without hypercalcemia, decreased carbon dioxide combining power, no azotemia and degeneration in the tubular epithelium.[2, 12] This con-

dition may be associated with cystinosis with or without cystinuria.[4] The treatment suggested for this rare condition is the same as that for other renal acidosis—alkali, high calcium intake and vitamin D. Both kinds of renal acidosis allow excess calcium loss in the urine, which gives rise to a tendency toward low serum calcium, which in turn causes secondary hyperparathyroidism.

Excess renal excretion of calcium is largely responsible for the osteomalacia caused by renal acidosis. Idiopathic hypercalcuria, however, is the most usual of the metabolic disorders causing hypercalcuria.[2] Many persons who are "stone-formers" have idiopathic hypercalcuria[7] and presumably there is a metabolic defect so that the kidneys excrete more calcium than they should for an otherwise normal serum calcium. In such cases there is no renal acidosis. The increased calcium loss leads to the same sequence of events as increased calcium loss from other causes and the end results are osteomalacia and nephrolithiasis or nephrocalcinosis. Treatment urologically should consist of the Shorr regimen to lower the phosphate-calcium intake. Simultaneous steroid therapy should stimulate the laying-down of calcium in the bone.

Immediately following the removal of a parathyroid tumor, osteomalacia may occur transiently due to the precipitous fall in calcium, but this is rare and may be prevented by giving adequate calcium.

Increased urinary calcium excretion by the kidney may also occur in patients with chronic pyelonephritis. The serum calcium level in this condition may be normal or low.

Milkman's syndrome[14] is osteomalacia of a special type in which there are ribbon-like zones of decalcification with pseudofractures rather than generalized bone disease. It can be caused by any of the causes of osteomalacia and the treatment is the same as for osteomalacia from any specific cause.

DISCUSSION

Urologically, the end results of hypercalcuria and all types of metabolic bone disease are identical—namely, nephrolithiasis and nephrocalcinosis. However, the differential diagnosis and proper identification of the primary lesion in each case of hypercalcuria and renal calcium precipitation will lead to appropriate treatment and prompt improvement. The first step is to recognize that hypercalcuria is present by measuring the calcium excretion while the patient follows a controlled diet.

Hypercalcuria due to increased gastrointestinal absorption of calcium leads to hypercalcuria as a direct result of the excess intake. The blood levels of calcium, phosphorus and alkaline phosphatase are generally normal and decreased calcium intake results in rapid improvement.

Hypercalcuria due to increased bone resorption occurs in a group of diseases of which primary hyperparathyroidism is the most prominent. In this syndrome, there is hypercalcuria, hypercalcemia and hypophosphatemia. If the bones are involved, the earliest lesions are in the skull and lamina dura and the alkaline phosphatase will be elevated. Surgical removal of the parathyroid tumor results in cure. Chronic acidosis causes secondary hyperparathyroidism or "renal rickets." In this disease, the serum is elevated, calcium is low or normal, there is acidosis and renal disease and there is always bone disease with a high phosphatase. Treatment is to lessen the acidosis and the renal disease and to give calcium and vitamin D for the bone lesions. Metastatic malignant disease of the osteolytic type causes hypercalcemia because of increased bone destruction. The roentgenographic findings are typical and the serum phosphorus is most often normal. Treatment of the underlying malignant disease and, in many instances the administration of steroid, will effect remission in the hypercalcuria. Multiple myeloma may cause hypercalcemia and hypercalcuria but the serum phosphorus and alkaline phosphatase are normal. In addition, there are a host of diagnostic points which occur typically in myeloma. Paget's disease causes a very pronounced elevation in the phosphatase but there is normal serum calcium and phosphorus. The roentgen evidence is typical. Immobilization of patients with Paget's disease is particularly dangerous, and strict reduction of the intake of calcium, phosphorus and vitamin D is necessary. Boeck's sarcoid produces bone lesions similar to those of hyperparathyroidism but the lesions are mostly limited to the hands and feet and have a typical punched-out appearance. The serum and urinary calcium levels are high but the serum phosphorus is normal and the alkaline phosphatase may be normal or high. The serum globulin and protein are elevated. Treatment includes reduction of calcium intake and administration of corticotropin and cortisone.

Hypercalcuria due to decreased bone formation occurs with either osteoporosis or osteomalacia. In osteoporosis, there is a defect in tissue metabolism so that the bones cannot accept the available calcium. The defect may be in the osteoblasts or the bone matrix or on an idiopathic basis. In recumbency, or postmenopausal, osteoporosis, the serum calcium and phosphorus may be high and the alkaline phosphatase is normal. The skull and lamina dura are normal. Treatment by the Shorr regimen, mobilization and weight-bearing will prevent renal complications. In postmenopausal osteoporosis, steroid therapy (estrogens and androgens) causes dramatic response. Defects in the bone matrix may occur in any state of protein deficit (malnutrition), scurvy, and conditions in which there is excess anti-

anabolic hormone (Cushing's syndrome, "alarm reaction," corticotropin and cortisone therapy). Treatment is directed at the underlying condition, and in addition a high protein diet is given and testosterone is administered. Senile osteoporosis responds rapidly to steroid therapy. The idiopathic variety is uncommon and does not respond to steroids.

Osteomalacia is a condition of calcium lack. In this condition the serum alkaline phosphatase is high and the serum calcium and phosphorus may be normal or low. It may occur from a lack of vitamin D (rare), because of an idiopathic loss of calcium in the urine, or secondary to renal acidosis. Idiopathic hypercalcuria should be treated by the Shorr regimen and possibly administration of steroids. Renal acidosis of the tubular insufficiency type is due to calcium loss in the urine. It is characterized by hyperchloremic acidosis with alkaline urine, decreased urinary ammonia and decreased titratable acidity. Treatment consists of a high alkali intake, and administration of calcium and vitamin D in large doses and the response to treatment is dramatic. Renal acidosis of the Fanconi type also is due to excess calcium loss in the urine and treatment is the same.

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